**PATENT APPLICATION**

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES**

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| In re Application of: | Docket No: **Q80490** |
| **Kazunari YAMAGUCHI *et al.*** | Conf. No.: **9623** |
| Appln. No.: **10/805,220** | Group Art Unit: **1648** |
| Filed: **March 22, 2004** | Examiner: **Chen, Stacy** |

For: **METHOD FOR DETECTING BORNA DISEASE VIRUS INFECTION**

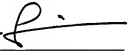
**SUBMISSION OF APPEAL BRIEF**

**MAIL STOP APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

Submitted herewith please find an Appeal Brief. The U.S. Patent and Trademark Office is directed and authorized to charge the statutory fee of $540.00 and all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,



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Date: May 22, 2009

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For: **METHOD FOR DETECTING BORNA DISEASE VIRUS INFECTION**

**APPEAL BRIEF UNDER 37 C.F.R. § 41.37**

**MAIL STOP APPEAL BRIEF - PATENTS**
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

In accordance with the provisions of 37 C.F.R. § 41.37, Appellant submits the following:

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## I. REAL PARTY IN INTEREST

The real party in interest is SYSMEX CORPORATION, Hyogo, Japan.

## II. RELATED APPEALS AND INTERFERENCES

There are not believed to be any other prior or pending appeals, interferences or judicial proceedings which are related to, will directly affect, or will be directly affected by or have a bearing on the Board's decision in the present appeal.

## III. STATUS OF CLAIMS

Claims 17, 24, 26 are pending in the application. Claims 1-16, 18-19, 20-23 and 25 are cancelled. All pending claims are currently rejected. This appeal is directed to rejected claims 17, 24 and 26.

## IV. STATUS OF AMENDMENTS

The Amendment Under 37 C.F.R. § 1.116 filed on December 19, 2008, was entered, as indicated in the Advisory Action mailed January 15, 2009.

## V. SUMMARY OF THE CLAIMED SUBJECT MATTER

Claims 17, 24, 26 are independent claims.

Independent claim 17 relates to a method of determining whether a subject has been infected with Borna disease virus (hereinafter, BDV). *See* paragraphs 51-54.[1] Appellant's method for determining whether a subject has been infected with BDV accordingly to claim 17 involves reacting immobilized p10 and p24 (p10 of SEQ ID NO:8 and p24 of SEQ ID NO:1, which are synthetic BDV proteins) with a sample from a living body. Specification, *inter alia*, page 13. If IgM and/or IgG antibodies to synthetic p10 and p24 are detected in the sample, it is determined that the subject from which the sample was obtained was infected with BDV. Specification, *inter alia*, pages 12 and 15.

Independent claim 24 also relates to a method of determining whether a subject has been infected with BDV but, this method involves reacting immobilized p10 and p40 (p10 of SEQ ID NO:8 and p40 of SEQ ID NO:3, synthetic BDV proteins) with a sample from a living body. Specification, *inter alia*, page 13. If IgM and/or IgG antibodies to p10 and p40 are detected in the sample, the subject from which the sample was obtained was infected with BDV. Specification, *inter alia*, pages 12 and 15.

Independent claim 26 relates to a method of determining whether a subject has been infected with BDV. The method involves reacting immobilized p10, p24 and p40 (p10 of SEQ ID NO:8, p24 of SEQ ID NO:1 and p40 of SEQ ID NO:3) with a sample from a living body.

[1] Citations are to the published specification, US 2004/0234955-A1.

Specification, *inter alia*, page 13. If IgM and/or IgG antibodies to p10, p24 and p40 are detected in the subject's sample, the subject from which the sample was obtained was infected with BDV. Specification, *inter alia*, pages 12 and 15.

## VI. GROUNDS OF REJECTION TO BE REVIEWED ON APPEAL

The sole ground of rejection on appeal is whether the Examiner erred in rejecting claims 17, 24 and 26 under 35 U.S.C. § 103(a) as being unpatentable over Yamaguchi *et al.* (*Ann. Clin. Biochem.* 2001, 38:348-355), in view of Watanabe *et al.* (*J. Vet. Med. Sci.*, 2000, 62(7):775-778,), Planz *et al.* (*Journal of Virology*, 1999, 73:6251-6256) and further in view of Hatalski *et al.* (*Journal of Virology*, February 1995, 69(2):741-747), and Carbone, K.M. (*Clin. Micro. Rev.*, 2001, 14(3):513-527).

## VII. ARGUMENT

The Examiner erred in rejecting claims 17, 24 and 26 under 35 U.S.C. § 103(a) over Yamaguchi *et al.* in view of Watanabe *et al.*, Planz *et al.*, Hatalski *et al.*, and Carbone. Appellants respectfully request the Board to reverse this rejection for at least the following reasons.

**A. The References Cited By The Office Fail To Teach Or Suggest Appellant's Methods Claimed in Claims 17, 24 and 26**

To maintain a rejection under 35 U.S.C. §103, the cited references must teach or suggest each and every element of the claim. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

**1. The Essential Elements of Claims 17, 24 and 26**

Independent claims 17, 24 and 26 recite methods of determining whether a subject has been infected with BDV. Specification, *inter alia*, page 8.

Appellant's method for determining whether a subject has been infected with BDV involves the steps of providing a support on which synthetic BDV proteins (i.e., peptides) are immobilized, reacting the immobilized synthetic peptides with a sample, and assaying for the presence of antibodies to the synthetic peptides. Specification, *inter alia*, pages 15-18.

Claim 17 recites a method wherein immobilized synthetic BDV derived p10 (SEQ ID NO:8) and p24 (SEQ ID NO:1) peptides are reacted with a sample. Claim 24 recites similar steps however, immobilized p10 and p40 (p40 of SEQ ID NO:3) are reacted. Claim 26 recites

steps similar to those recited in claims 17 and 24 however, immobilized p10 (SEQ ID NO:8), p24 and p40 are reacted. Thus, all three recited methods use p10 synthetic peptide (SEQ ID NO:8). In claims 17, 24 and 26, if IgM and/or IgG antibodies to the recited synthetic proteins are detected, the subject from which the sample was obtained has been infected with BDV.

**2. The References, Taken Alone Or Combined, Fail to Teach or Suggest The Essential Elements of Appellant's Claims 17, 24 and 26**

The library of references as cited by the Office fail to teach or suggest, either alone or in combination, the subject matter of claims 17, 24 and 26 for the following reasons.

**a. Yamaguchi *et al.* Fail to Disclose Essential Elements of Appellant's Claims 17, 24 and 26**

Yamaguchi *et al.* is titled, "Synthetic peptide-based electrochemiluminescence immunoassay for anti-Borna disease virus p40 and p24 antibodies in rat and horse serum," and describes an assay (abbreviated ECLIA) for detecting antibodies to BDV using synthetic peptides. Yamaguchi *et al.*, abstract. The reference discloses using synthetic p24 and p40 peptides. Yamaguchi *et al.*, page 349, Table 1.

Yamaguchi *et al.* fail to teach or suggest synthetic p10 peptides or peptides having SEQ ID NO:8. Yamaguchi *et al.* fail to disclose assaying for BDV IgM antibodies. Yamaguchi *et al.*, page 352, "Detection of antibodies to BDV peptides in rat serum samples."

**b. Watanabe *et al.* Fail to Disclose Essential Elements of Appellant's Claims 17, 24 and 26**

Watanabe *et al.* is titled, "Antibodies to Borna disease virus in infected adult rats: an early appearance of anti-p10 antibody and recognition of novel virus-specific proteins in infected animal brain cells," and discloses antibodies to viral p10, p24 and p40 in rats inoculated with BDV. Watanabe *et al.*, Abstract.

Watanabe *et al.* do not teach or suggest a synthetic peptide based BDV method. Watanabe *et al.* also fail to teach or suggest detecting IgM and/or IgG antibodies to BDV. Watanabe *et al.* fail to disclose Appellant's SEQ ID NOs:1, 3 or 8.

**c. Planz *et al.* Fail to Disclose Essential Elements of Appellant's Claims 17, 24 and 26**

Planz *et al.* is titled, "Pathogenesis of Borna Disease Virus: Granulocyte Fractions of Psychiatric Patients Harbor Infectious Virus in the Absence of Antiviral Antibodies."

Planz *et al.* fail to disclose antibodies to BDV or detection thereof. Planz *et al.*, Abstract and page 6,253, Table 2 (*see* BDV-specific antibodies by: WB and IP). Planz *et al.* fail to disclose a solid phase assay in which IgM and/or IgG antibodies to BDV are detectable. *Id.* The reference fail to disclose Appellant's SEQ ID NOs:1, 3 and 8.

**d. Hatalski *et al.* Fail to Disclose Essential Elements of Appellant's Claims 17, 24 and 26**

Hatalski *et al.* is titled, "Neutralizing antibodies in Borna disease virus-infected rats," and disclose that as a result of infection by BVD antibodies are formed to viral gp18, gp23 and gp40.

Hatalski *et al.* fail to disclose synthetic peptides, including a synthetic p10. The reference fail to disclose Appellant's SEQ ID NOs:1, 3 and 8.

**e. Carbone Fails to Disclose Essential Elements of Appellant's Claims 17, 24 and 26**

Carbone is titled, "Borna Disease Virus and Human Disease," and discloses the controversy and numerous technical difficulties in assaying for BDV infection. Carbone, page 513, Introduction.

Carbone fails to disclose synthetic peptides for assaying IgM and/or IgG antibodies to BDV. Carbone fails to disclose Appellant's SEQ ID NOs 1, 3 and 8.

Thus, the combined teachings of Watanabe *et al.*, Hatalski *et al.* and Carbone fail to provide the motivation to modify Yamaguchi *et al.*'s ECLIA method to include synthetic p10 peptides or p10 antibodies and fails to provide the motivation to examine both IgM and IgG antibodies in Appellant's assay. Further, for the reasons discussed in detail below, Appellant submits that the references, in fact, teach away from Appellant's invention. The present invention also demonstrates unexpected superior results over Yamaguchi *et al.*'s method for the following reasons.

**B. The Office Fails to Set Forth A Reason Supported by A Rational Underpinning That Would Have Prompted One Of Ordinary Skill To Combine The Elements The Way Appellant's Invention Does**

To maintain a case of obviousness under 35 U.S.C. §103, it is necessary to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007). Rejections on obviousness grounds cannot be sustained by mere conclusory statements; instead, there must be some articulated reasoning with some rational

underpinning to support and sustain a conclusion of obviousness. *Id.* Use of hindsight is improper in determining obviousness. *Id.*

**1. The Office Improperly Relied Upon Hindsight Conclusory Statements To Maintain The Obviousness Rejection of Appellant's Claims 17, 24 and 26**

It is impossible for the Office to identify a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does because essential elements of Appellant's claimed invention are not disclosed or suggested by the references. *See* Section VII A, *infra.*

Assuming *arguendo* that all of the elements of Appellant's claimed invention are taught or suggested, *which they are not*, the Office provides conclusory statements based on hindsight as a substitute for reasoning for combining various pieces of information (information that appears to either be present in the references or obtained from additional undisclosed sources). Rejections on obviousness grounds cannot be sustained by mere hindsight conclusory statements.

For example, the Office concludes that one of ordinary skill in the art would have been motivated by Watanabe et al.'s reference to BDV viral proteins to utilize p10 synthetic peptides and p10 antibodies to increase the sensitivity of Yamaguchi *et al.*'s method. Advisory Action of January 15, 2009, page 2. The Office further concludes that the motivation to modify Yamaguchi *et al.*'s method comes from the improved diagnostic method that would result from increasing the sensitivity of Yamaguchi *et al.*'s method by detecting anti-p10 antibodies in addition to anti-p24 and anti-p40 antibodies. Advisory Action of January 15, 2009, page 2. These conclusions are unsupported.

Watanabe *et al.* contains information regarding BDV viral proteins, not synthetic peptides. Watanabe *et al.* does not disclose the synthetic peptides corresponding to SEQ ID NOs:1, 3, and 8, recited elements in Appellant's claims. Watanabe *et al.* fail to disclose detecting IgM and/or IgG antibodies to BDV, essential features of Appellant's invention. The improved diagnostic method having an increased sensitivity referred to by the Office do not exist but appear to be mere speculation. There is no suggestion to combine Yamaguchi *et al.*'s assay to include detection of synthetic peptide p10 corresponding to SEQ ID NO:8 except from using Appellant's invention as a template through a hindsight reconstruction of Appellant's claims.

Appellants previously pointed out that one having ordinary skill understands that adding additional BDV antigens in a diagnostic method could compromise the specificity of the assay unless the antigen is carefully selected by examining its expression profile and the cross reactivity of the antibody raised against the antigen.[2] Thus, mention of BDV viral proteins is not motivation to include more synthetic peptides in an assay, yet the Office has not addressed this.

The Office alleges the reference states, "antibodies to individual viral proteins and BDV specific antigens are useful for establishing diagnostic methods", which is inaccurate and misinterprets the reference. Advisory Action of January 15, 2009, page 2. Watanabe *et al.*

[2] The record reflects that Appellants pointed out, and the Office failed to challenge, that the validity of a diagnostic test can be determined by measuring the rate of sensitivity (true-negative rate) and specificity (true-positive rate) (Carbone *et al.*, Page 515, Column 2, line 47-50) thus, it is equally important to improve the specificity of diagnostic tests in order to minimize false positives to prevent unnecessary treatment. Additionally, Appellants pointed out that BDV expresses 6 classes of proteins (N,P,M,G,L, and p10) which undergo distinct secondary modifications (i.e., glycosylation and phosphorylation) and that the viral proteins form distinct heteromeric complexes (Carbone *et al.*, Page 514, Column 1, line 27-31). *See* Amendment Under 37 C.F.R. § 1.116, December 19, 2008, page 8.

prophetically states, "the results in this study *could be worthy* for establishment of diagnostics method for BDV infection." [Emphasis added.] Watanabe, page 777, column 2. This is nothing more than conjecture.

The Office's use of hindsight in making the rejection is made more apparent in light of Yamaguchi *et al.* Yamaguchi *et al.* underscores the difficulty in diagnosis of BDV infection. Yamaguchi *et al.* state, "IFA does not always give definite results, due to the existence of cell specific auto-antibodies, the variability of subjective interpretation, and insufficient sensitivity in detecting low titer antibodies." Yamaguchi *et al.*, page 349, column 1. The reference states, "although IP and WB analyses may be more reliable and specific than IFA, these methods are time consuming and expensive and therefore unsuitable for large-scale screening." Yamaguchi *et al.*, page 349, column 1.

Another conclusion offered as a rationale by the Office is that because Hatalski *et al.* describes that IgM is detectable in response to BDV infection, and because Carbone indicates that IgM is sometimes serological evidence of BDV infection, testing for the presence of IgM and IgG would have worked in Yamaguchi *et al.*'s ECLIA method. This conclusion is offered as proof that Appellant's method is rendered obvious. Again, the conclusions lack support and are not suggested by the references.

Neither Hatalski *et al.* nor Carbone teaches or suggests detecting IgM and/or IgG following BDV infection. Carbone refers to detection of anti-BDV IgG antibodies at the convalescent-phase. It is known in the art that IgM antibodies are the first class of antibodies that are made in response to infection (Carbone, page 516, Column 1, line 27-30). However, one of

skill knows that most IgM antibodies quickly disappear, approximately one month after their appearance, and are replaced by IgG antibodies. Specification, page 2, the first paragraph. Thus, the detection of IgG antibodies alone is known in determining infection by BDV since IgM antibodies were thought to be absent. In addition, Carbone states (and one having ordinary skill would understand) that it is unlikely to obtain acute phase serum in natural BDV infections. Carbone, page 516, column 1, line 37-40.

Despite this information, the Office maintains that IgM and/or IgG would have worked in Yamaguchi *et al.*'s method and, because both antibodies would have worked Appellant's invention is obvious. There is no suggestion to combine Yamaguchi *et al.*'s assay to detect IgM and IgG except from employing, as the Office has done, impermissible hindsight.

Because conclusions cannot substitute for a reason that would have prompted a person of ordinary skill in the relevant field to combine the elements in the way the claimed new invention does, and because hindsight alone was employed in the obviousness analysis, the rejection should be withdrawn.

**2. The Unpredictable Art of BDV Detection Is Improperly Accorded No Weight By the Office In Considering the Patentability of Claims 17, 24 and 26**

Under 35 U.S.C. §103, the combination of familiar elements according to known methods is likely to be obvious when it does no more than yield *predictable* results. As reiterated by the Supreme Court, an analysis for determining obviousness must include analysis of the underlying factual inquiries including, (1) determining the scope and content of the prior art; (2) ascertaining the differences between the claimed invention and the prior art; and (3) resolving the

level of ordinary skill in the pertinent art. *KSR International Co. v. Teleflex Inc.*, 550 U.S. 398 (2007).

Based on this law, the Office established Guidelines that should be followed in making an obviousness determination. The Guidelines indicate the following rationales are indicative of obviousness: (a) combining prior art elements according to known methods to yield *predictable* results; (b) simple substitution of one known element for another to obtain *predictable* results; (c) use of a known technique to improve similar devices (methods, or products) in the same way; (d) applying a known technique to a known device (method, or product) ready for improvement to yield *predictable* results; (e) "Obvious to try"—choosing from a finite number of identified, *predictable* solutions, with a reasonable expectation of success; (f) known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been *predictable* to one of ordinary skill in the art; (g) some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention. Thus, according to the law and Office Guidelines, predictability is a key determinant in an obviousness analysis, particularly in an unpredictable art such as the art of using biological assays for the detection of BDV infection.

In making the obviousness rejection, the Office failed to appreciate that the art of BDV detection is highly unpredictable. The references *cited by the Office* indicate that such is the case.

Diagnostic BDV tests are discussed in Carbone in detail, *inter alia*, at pages 515 to 520. Carbone clearly indicates, "BDV infection is complex and the infectious stage is unpredictable to

know." Carbone, page 516, column 2. Regarding Immunoflourescence Assays, Carbone indicates, "the major technical concerns with the IFA technique are specificity and the variability introduced by reader expertise (i.e., correct recognition of the specific, characteristic pattern of BDV antigens in the infected cell" and "...reader to reader variability in testing makes it difficult or impossible to replicate serology results among independent laboratories." Carbone, page 518, column 1. Regarding Immunoblot Assays, Carbone states, "although not proven for BDV proteins, both nonhuman glycosylation patterns of virus antigens as well as the typical protein-reducing and -denaturing characteristics of the gel can destroy or alter conformational virus epitopes." Carbone, page 518, column 2, paragraph 3. Carbone continues, "drawbacks of the IB technique include the time-consuming and costly nature of this technique and the disadvantage that the high specificity screen with IB may be accompanied by some decrease in sensitivity of the test." Carbone, page 518, column 2, first paragraph.

Regarding ELISA, Carbone states, "BDV-specific ELISAs have been reported to have some difficulty with sensitivity" and "it is unclear whether the inability of these ELISAs to detect anti-BDV antibody in humans, where anti-BDV antibody titers are generally low, represents a false-negative due to species specific variability in the sensitivity of the ELISA or a true-negative result...", "specificity concerns with these ELISAs are demonstrated when human sera shown seronegative by IB give a positive result in ELISA due to non-specific reactivity." Carbone, page 518, column 2, second full paragraph. As to molecular diagnostic methods, Carbone states, "the presence of RT-PCR inhibitors, such as heparin or hemoglobin in an blood sample, may result in false-negative results." Carbone, page 520, third full paragraph. Carbone

also indicates, "a low level of viral RNA in peripheral blood may fall below the detection sensitivity of RT-PCR and produce false negative results." The reference states, the "ability of BDV primers designed from animal virus sequences to recognize a putative human BDV also needs to be taken into account" and is therefore yet another factor contributing to the unpredictability of diagnosis. Carbone, page 520, first column, last paragraph.

Regarding confirmation of a potentially positive test result, Carbone states, "using the sequence to confirm the source of the recovered strain, e.g., to discinguish a human BDV strain from a laboratory contaminant, is not feasible at present." Carbone, page 520, second column, third full paragraph. Confirmation is also unpredictable due to BDV being a "cell-associated virus, and it is difficult to recover infectious virus from bodily fluids." Carbone, page 520, column 2, fourth paragraph. Further, infectious virus isolation testing is unpredictable because of "...the low level of infectious BDV replication in some species (probably including humans)." Carbone pages 520-521, last paragraph. Carbone states, as a conclusion of the research, "what *is needed first* is a validated assay or series of assays that are capable of reliably identifying BDV infection in humans." [Emphasis added.] Carbone, page 523, second column, fourth full paragraph.

Yamaguchi *et al.* also underscores the unpredictability in diagnosis of BDV infection. For example, Yamaguchi *et al.* state, "IFA does not always give definite results, due to the existence of cell specific auto-antibodies, the variability of subjective interpretation, and insufficient sensitivity in detecting low titer antibodies." Yamaguchi *et al.*, page 349, column 1. The reference states, "although IP and WB analyses may be more reliable and specific than IFA,

these methods are time consuming and expensive and therefore unsuitable for large-scale screening." Yamaguchi *et al.*, page 349, column 1.

The Office overlooked significant passages of Planz *et al.* which underscore the unpredictability in BDV diagnosis relevant to the patentability of Appellant's claimed invention. For example, the Examiner ignored the statement, "due to conflicting results obtained in attempts to detect viral nucleic acid consistently in human blood from psychiatric patients, this issue is still controversial." Planz *et al.*, page 6251, column 1. Furthermore, Planz *et al.* disclose, "sera were obtained from all three patients and tested either in Western blot analysis or by immunofluorescence for the presence of BDV specific antibodies" and "interestingly, in these sera, no virus specific antibodies could be detected, even at dilutions of 1:2 in immunofluorescence." Planz *et al.*, page 6255, first column, first paragraph. The title of the paper also rebuts the Examiner's position indicating infection of the granulocyte fraction absent antibodies. The observations in Planz *et al.* rebut the Examiner's conclusion of obviousness.

Regarding Hatalski *et al.*, the reference reveals the unpredictability in the field of BDV diagnosis. For example, Hatalski *et al.* fail to identify p10 as being important in BDV infection detection. Hatalski *et al.*, page 741, first column. Hatalski *et al.* focus the attention of one having ordinary skill in the art to gp18, not p10. Hatalski *et al.*, page 741, first column. Hatalski *et al.* state, "the presence or absence of neutralizing antibodies in BDV-infected animals has been controversial…some reports have not shown evidence for neutralizing antibodies; however, this may reflect different time points for collection of sera or variation in the assay system for neutralization." Hatalski *et al.*, page 744-745, second column, Discussion. Hatalski *et al.*

indicates, "there are several plausible explanations for the late appearance of neutralizing antibodies in Borna disease. One possibility is that, in the early disease, gp18 is expressed at lower levels than the 40- and 23-kDa viral proteins, which elicit high titer antibodies" and " the role of neutralizing antibodies in Borna disease is less clear, given [that] the central nervous system viral titers remain elevated in the presence of neutralizing antibodies in serum and cerebrospinal fluid." Hatalski *et al.*, page 745, second column, last paragraph.

The law and Office Guidelines were not properly applied in making the obviousness rejection because the unpredictable nature of BDV detection, as illustrated in the above mentioned quotes from references cited by the Office, was largely ignored. Predictability is a key determinant in an obviousness analysis, particularly in an unpredictable art such as BDV detection, yet the Office failed to accord proper weight to this evidence. For this reason alone, the rejection should be withdrawn.

**B. The Office Failed To Appreciate Numerous Teachings Away From Appellant's Claims 17, 24 and 26**

It is well-settled law that a *prima facie* case of obviousness may be rebutted by showing that the art, in any material respect, teaches away from the claimed invention. See *In re Geisler*, 116 F.3d 1465, 1471, 43 USPQ2d 1362, 1366 (Fed. Cir. 1997). A reference teaches away when a person of ordinary skill in the art, upon reading it, would be discouraged from following the path set out in the reference, or would be led in a path divergent from the path taken by the inventor. See *Monarch Knitting Mach. Corp v. Sulzer Morat Gmbh*, 139 F.3d, 877, 45 USPQ2d 1977 (Fed. Cir. 1998); *Para-Ordnance Mfg. v. SGS Importers Int'l Inc.*, 73 F.3d1085, 37

USPQ2d 1237 (Fed. Cir. 1995); and *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994). "[W]hen the prior art teaches away from the claimed solution...obviousness cannot be proven merely by showing that a known composition could have been modified by routine experimentation or solely on the expectation of success; it must be shown that those of ordinary skill in the art would have had some apparent reason to modify the known composition in a way that would result in the claimed composition." *Ex parte Whalen* (Bd. Pat. App. & Int., July 23, 2008).

The record is replete with instances wherein the references teach away from Appellant's claimed invention. Yamaguchi *et al.* teach away from the combination suggested by the Office, because the reference definitively states, "the p40 and p20, expressed at high levels in the rat brain and infected cells, represent good markers with which to search for evidence of BDV infection in animal and human cells." Yamaguchi *et al.*, page 354, column 1. Therefore, according to Yamaguchi *et al.* in 2001, one of ordinary skill in the art would have reasonably expected that p40 and p20 assays alone were sufficient diagnostic assays making an appreciation of adding p10 highly unreasonable and contrary to common sense. The teaching away in Yamaguchi *et al.* is stark when compared to Appellant's comparative data, which teaches, in Comparative Example 1, dramatic improvement of BDV detection when p10 antibodies are included in the assay. Specification, pages 22-25, Table 1. Appellant's Table 1 teaches that 17 out of 23 specimens (73.9%) were positive for BDV infection when p24 and p40 antibodies were used in the assay but that by including p10 antibodies the results increase to 95.7%. In addition, 5 out of 23 specimens were detected with p10 antibodies but not with p24 nor with p40 antibodies alone.

Regarding Planz et al., the title of the paper alone rebuts the Examiner's position - the title plainly indicates BDV infection absent antibodies. Planz *et al.* provide data that detection of BDV infection occurs without IgM and IgG antibodies to BDV. Planz *et al.*, Abstract and page 6,253, Table 2 (*see* BDV-specific antibodies by: WB and IP). Planz *et al.* concludes, "we were able to demonstrate the presence of infectious BDV in the cell fraction harboring granulocytes, a finding that is important for further strategies of diagnosis and also provides an explanation of controversial results obtained in the past." Planz *et al.*, page 6255, second column, last full paragraph. Planz *et al.* fail to disclose a solid phase assay in which IgM and/or IgG antibodies to BDV are detectable. Id. The reference fails to disclose Appellant's SEQ ID NOs:1, 3 and 8. The observations in Planz *et al.* rebut the Examiner's conclusion of obviousness because Planz *et al.* teach away from the use of antibody based detection methods of BDV in favor of nucleic acid methods.

Hatalski *et al.* also teaches away from Appellant's claimed invention. Hatalski *et al.* fail to identify p10 as being important in BDV infection detection. Hatalski *et al.*, page 741, first column. Hatalski *et al.* instead focus the attention of one having ordinary skill in the art to gp18, not p10. Hatalski *et al.*, page 741, first column. A person of ordinary skill in the art having common sense at the time of the invention would not have reasonably viewed Haltaski *et al.* and become motivated to include p10.

Carbone teaches away from methods using IgM and IgG detection. Carbone does not disclose use of IgM antibodies in determining infection by BDV. The reference indicates, rather, that one of ordinary skill in the art would reasonably expect that IgM antibodies to BDV, if

detectable, quickly disappear, approximately one month after their appearance, and are replaced by IgG antibodies. Specification, page 2, the whole 1st paragraph. Thus, one of ordinary skill in the art would understand that Carbone suggests, if anything, a method of detecting IgG alone, particularly since, accordingly to the reference, it is not always possible to obtain acute phase serum in natural BDV infections. Carbone, page 516, column 1, line 37-40.

The library of references cited by the Office makes clear that a person of ordinary skill in the art, upon reading the reference, would be led down a different path from the path taken by Appellant. In view of the information in the references, Appellant's method is non-obvious and the rejection should be withdrawn.

**C. The Office Failed To Appreciate Appellant's Unexpected Superior Results of the Methods of Claims 17, 24 and 26**

A *prima facie* case of obviousness may be rebutted by a showing of unexpectedly superior properties of the claimed invention compared to the closest prior art which is commensurate with the claims. *Kao Corp. v. Unilever United. States Inc.*, 441 F.3d 963 (Fed. Cir. 2006). For unexpectedly superior properties, the comparison is made to the closest specifically disclosed composition/method of one piece of prior art, not with the combination of art used as the basis for the rejection. *In Re Baxter Travenol Labs.*, 952 F.2d 388, 392 (Fed. Cir. 1991).

The instant specification discloses unexpected results. One unexpectedly superior result is based on the unexpected appreciation that it requires an unusually long period of time for antibody class switching (i.e., going from IgM to IgG) to occur when antibodies to BDV are

made (Page 31, line 1-4). Specifically, Appellant demonstrates that IgM antibodies are detected even one year after BDV infection (page 12, line 17-22). Thus, the unexpected property of the IgM antibodies disclosed by Appellant allows one to examine the presence of both IgM and IgG not only at the early phase but also at the later phase of BDV infection. Given the unexpected kinetics of IgM antibodies raised by BDV infection, Appellant submits that it is unlikely that one of ordinary skill in the art would have had a reasonable expectation that testing both IgM and IgG antibodies would increase the sensitivity in detecting an infection absent the knowledge from Appellant's disclosure.

Appellant acknowledges that it might be difficult to determine if a subject is actively or latently infected with BDV based upon the detection of the antibodies as disclosed in the present invention. However, contrary to the Examiner's assertion, the objective of the present invention is not determining whether a subject is in an active or a cleared state of BDV infection. Rather, the present invention is directed to "a method for detecting whether a subject has been infected with Borna Disease Virus" as recited in Claims 17, 24 and 26.

Further, Appellant submits that the present invention provides unexpectedly superior results over Yamaguchi *et al.*'s ECLIA method, the Office's primary reference. Comparative Example 1 of the instant specification demonstrates improvement of BDV detection rate when p10 antibodies are included in the assay in comparison to the method detecting p24 and p40 antigens, e.g., Yamaguchi *et al.* (pages 22-25, Table 1). Specifically, Table 1 shows that 17 out of 23 specimens (73.9%) are detected as positive for BDV infection when p24 and p40 antibodies are used in the assay. In contrast, the data show that the BDV detection rate increases

to 95.7% (22 out of 23 specimens) when p10 antibodies are included in the method. Importantly, 5 out of 23 specimens were detected with p10 antibodies but not with p24 nor with p40 antibodies indicating that the detection of p10 increases the sensitivity of the BDV detection method without compromising the specificity of the assay.

Together, the information in these references would not have and could not have led one of ordinary skill in the art to achieve the subject matter of claims 17, 24 and 26. The combined teachings of Watanabe *et al.*, Hatalski *et al.* and Carbone fail to provide the motivation to modify Yamaguchi *et al.*'s ECLIA method to include the p10 antibody and to examine both IgM and IgG antibodies in the assay and in fact teach away. Furthermore, Appellant submits that the present invention demonstrates unexpected superior results over Yamaguchi *et al.*'s method.

Accordingly, in view of foregoing, Appellant submits that the present invention is not obvious over cited references under 35 U.S.C. § 103(a).

For the reasons discussed above, Appellants respectfully request the Board to reverse the rejection of claims 17, 24 and 26.

The U.S. Patent and Trademark Office is directed and authorized to charge the statutory fee (37 C.F.R. §41.37(a) and 1.17(c)) and all required fees, except for the Issue Fee and the Publication Fee, to Deposit Account No. 19-4880. Please also credit any overpayments to said Deposit Account.

Respectfully submitted,

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## CLAIMS APPENDIX

CLAIMS 17, 24 and 26 ARE ON APPEAL:

Claim 17. (previously presented) A method for determining whether a subject has been infected with Borna disease virus (BDV), comprising:

(a) providing a support having immobilized thereon p10 BDV synthetic antigen polypeptide and p24 BDV synthetic antigen polypeptide;

(b) reacting the resulting support with a sample from a living body; and

(c) assaying for both anti-BDV IgM antibody and anti-BDV IgG antibody which bind to said p10 BDV synthetic antigen polypeptide and said p24 BDV synthetic antigen polypeptide immobilized on said support, so as to detect said anti-BDV IgM antibody and/or anti-BDV IgG antibody in said sample, wherein said subject is determined to have been infected with BDV when said anti-BDV IgM antibody or said anti-BDV IgG antibody, or both said anti-BDV IgM antibody and said anti-BDV IgG antibody is detected,

wherein the p10 BDV synthetic antigen polypeptide has an amino acid sequence as set forth in SEQ ID NO: 8,

wherein the p24 BDV synthetic antigen polypeptide has an amino acid sequence as set forth in SEQ ID NO: 1.

Claim 24. (previously presented) A method for determining whether a subject has been infected with Borna disease virus (BDV), comprising:

(a) providing a support having immobilized thereon p10 BDV synthetic antigen polypeptide and p40 BDV synthetic antigen polypeptide;

(b) reacting the resulting support with a sample from a living body; and

(c) assaying for both anti-BDV IgM antibody and anti-BDV IgG antibody which bind to said p10 BDV synthetic antigen polypeptide and said p40 BDV synthetic antigen polypeptide immobilized on said support, so as to detect said anti-BDV IgM antibody and/or anti-BDV IgG antibody in said sample, wherein said subject is determined to have been infected with BDV when the said anti-BDV IgM antibody or the said anti-BDV IgG antibody, or both the said anti-BDV IgM antibody and the said anti-BDV IgG antibody is detected,

wherein the p10 BDV synthetic antigen polypeptide has an amino acid sequence as set forth in SEQ ID NO: 8,

wherein the p40 BDV synthetic antigen polypeptide has an amino acid sequence as set forth in SEQ ID NO: 3.

Claim 26. (previously presented) A method for determining whether a subject has been infected with Borna disease virus (BDV), comprising:

(a) providing a support having immobilized thereon p10 BDV synthetic antigen polypeptide, p24 BDV synthetic antigen polypeptide and p40 BDV synthetic antigen polypeptide;

(b) reacting the resulting support with a sample from a living body; and

(c) assaying for both anti-BDV IgM antibody and anti-BDV IgG antibody which bind to said p10 BDV synthetic antigen polypeptide, said p24 BDV synthetic antigen polypeptide and said p40 BDV synthetic antigen polypeptide immobilized on said support, so as to detect said anti-BDV IgM antibody and/or anti-BDV IgG antibody in said sample, wherein said subject is determined to have been infected with BDV infection is detected in said subject when the said anti-BDV IgM antibody or the said anti-BDV IgG antibody, or both the said anti-BDV IgM and the said anti-BDV IgG antibody is detected,

wherein the p10 BDV synthetic antigen polypeptide has an amino acid sequence as set forth in SEQ ID NO: 8,

wherein the p24 BDV synthetic antigen polypeptide has an amino acid sequence as set forth in SEQ ID NO: 1,

wherein the p40 BDV synthetic antigen polypeptide has an amino acid sequence as set forth in SEQ ID NO: 3.

## EVIDENCE APPENDIX:

NONE

## RELATED PROCEEDINGS APPENDIX

NONE